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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,409	11/28/2000	Clay B. Siegall	9632-014	9908

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PENNIE AND EDMONDS
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/12/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,409	SIEGALL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *10-20 and 38-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *10,11,15,38,50,51,59,60 and 63* is/are allowed.

6)☐ Claim(s) *12-14,16-20,39-44,46-49,52-58,61 and 62* is/are rejected.

7)☐ Claim(s) *45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 10-14, 16, 17, 19, 20, 38-46, 50-54 and 60 have been amended. Claim 63 has been added. Claims 10-20 and 38-63 are pending and under consideration.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, lines 12 and 33; page 32, line 5 and page 46, lines 1 and 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. Claim 45 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 15. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 45 is dependent on claim 38, however, the scope of claim 45 is identical to the scope of claim 15.

5. Claims 16 and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "highly stringent" in claim 16 is a relative term which renders the claim indefinite. The term "highly stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification sets forth on page 36,line 33 to page 37, line 8 an example of high stringency but states that this example is "by way of example and not limitation". Therefore this recitation is an embodiment of high stringency but not a definition of high stringency. Without a definition of high stringency the metes and bounds of the claims cannot be determined because it is not

possible to discern from the specification the precise limitation of high stringency versus hybridization conditions which are less than "high stringency".

6. Claims 12, 14, 17, 19, 43, 44 and 52-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claims 12, 14, 17, 19, 43 and 44 depend on the hybridoma deposited under accession number PTA-110 for enablement. Claims 53-54 are included in the rejection as they depend on claim 14. Claims 55-58 are included in this rejection as they depend on claim 43.

Applicant's referral to the deposit of the hybridoma secreting the S2C6 antibody on page 58 of the specification is insufficient assurance that all the conditions of 37 CFR 1.801-1.809 have been met.

It is noted that the deposit was made under the provisions of the Budapest Treaty, therefore, the filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

7. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention. Claim 49 embodies the isolated nucleic acid of claim 46, wherein the antibody is a human antibody..

The art teaches the screening of human immunoglobulin libraries for antibodies that bind specific antigens (Clark, Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, pp. 4-5). The art does not teach the selection of antibodies which bind to a specific antigen, wherein said antibodies would have a specific amino acid sequence in the variable chains or CDR. It is noted that the antibodies are screened for binding specificities not for amino acid sequence. There are no teaching in the art or the specification on how to make a human antibody comprising the instant CDR or specific variable chain regions and it is unclear if the human immunoglobulin repertoire would even have the claimed amino acid sequences of the murine S2C6 antibody. The specification provides no teachings addressing these concerns and no teachings specifically drawn to how to make a human antibody comprising the required amino acid sequences. It flows logically from this, that if one of skill in the art cannot make the antibodies, one cannot make the nucleic acid encoding said antibodies. Given the state of the art and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to make the claimed isolated nucleic acid encoding the human antibodies.

8. Claims 13, 16, 39, 40, 41, 42, 46-49 and 52-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to molecules without structural characterization

Claim 42 is drawn to an isolated nucleic acid comprising a nucleotide sequence encoding an antibody heavy chain, which antibody binds to CD40, increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. Claims 52-54 are dependent on claim 42.

When given the broadest reasonable interpretation the claims encompass nucleic acids encoding antibodies which bind to an epitope of CD40 which is not the epitope to which the

S2C6 antibody binds. The genus of antibodies encompasses molecules which do not comprising antigen-binding portions of the S2C6 antibody and which do not bind to CD40 at the same epitope as the S2C6 antibody. Thus the genus of molecules is highly variant encompassing antibodies which have unlimited structural alterations from the disclosed variable chains and CDR regions of the S2C6 antibody, and which have functional attributes which differ from the S2C6 antibody, such as binding to an CD40 epitope which differs from the S2C6 epitope. The disclosure of the S2C6 antibody does not adequately describe this genus of molecules because the genus encompasses members having structural and functional attributes which vary from the structural and functional attributes of the S2C6 antibody. One of skill in the art would reasonably conclude that applicant was not in possession of the genus of antibodies on which the claimed method depends, therefore the nucleic acids encoding said antibodies lack adequate written description.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. In the instant case, the written description set forth only the isolated nucleic acid encoding the heavy and light chains of the S2C6 antibody. The specification further defines the CDR associated with said heavy and light chains. However, no other antibody which binds to CD40 is described.

(B)As drawn to isolated nucleic acids encoding protein variants of SEQ ID NO:7-10 and isolated nucleic acids which hybridizes under stringent conditions to the complement of SEQ ID NO:7.

Claim 13 is drawn to an isolated nucleotide sequence encoding an amino acid sequence having at least 95% identity to SEQ ID NO:7 and which binds to CD40. Claims 55-58 are dependent on claim 13. Claim 16 is drawn to an isolated nucleic acid sequence which hybridizes to the complement of SEQ ID NO:7, wherein said nucleic cid sequence encodes a protein which binds to CD40. Claim 39 is drawn to an isolated nucleic acid sequence encoding a protein having at least 95% identity to SEQ IDNO:7, which protein binds CD40 and comprises a human immunoglobulin domain. Claim 40 is drawn to an isolated nucleic acid encoding a protein having at least 80% identity to SEQ ID NO:8, 9 and 10, which protein binds to CD40 and comprises a human immunoglobulin constant domain. Claims 46-49 are dependent on claims 39 and 40.

When given the broadest reasonable interpretation, the claimed isolated nucleic acids rely upon a genus of antibodies which vary from the variable chain and CDR structure of the S2C6 antibody and which encompass different functional attributes of S2C6 because the claims are not limited to isolated nucleic acids encoding those antibodies which bind to the same epitope of CD40 as S2C6. It is noted that claims drawn to nucleic acids which hybridize to the complement of SEQ ID NO:7 under conditions of high stringency are not structurally defined because the metes and bounds of the term "high stringency" cannot be determined for the

reasons set forth in the rejection under 112, second above. Thus the claims rely upon a genus of antibodies which are structurally and functionally variant. The disclosure of the S2C6 antibody does not adequately describe this genus because the genus permits members having different structural and functional attributes from the S2C6 antibody. One of skill in the art would reasonably conclude that applicant was not in possession of the genus of antibodies on which the claimed isolated nucleic acids depends, therefore the claims lack adequate written description.

9. Claims 17-20, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant cells in vitro and recombinant cells in vivo within a transgenic mouse, does not reasonably provide enablement recombinant cells in vivo wherein said cell is within a transgenic animal which is not a mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification contemplates on page 10, lines 4-10 that the invention relates to a transgenic non-human animal containing one or more transgenes encoding a protein, which protein competes for binding to CD40 with monoclonal antibody S2C6. The specification further contemplates on page 17, lines 27-33 that the expression of the S2C6 genes can be carried out in transgenic non-human animals

It is recognized in the art, that although the technology developed to generate transgenic mice is becoming predictable and reliable, the application of this technology to other animals is difficult and unreliable. The abstract of Charreau et al (Transgene Research, 1996, Vol. 5, pp. 223-234) teaches that although the procedure of microinjection into fertilized rat ova is an established procedure, transgenic rats remain difficult to produce in comparison with mice, and that fewer than 20 transgenic rat lines have become established by 1996. The abstract of Nancarrow et al (Methods in Molecular Biology, 1993, vol. 18, pp. 273-303) acknowledges that the production of transgenic sheep has proved to be very difficult compared to the production of transgenic mice. The abstract of Machaty et al (Cloning Stem Cells, ~~202~~ 2002, Vol. 4, pp. 21-27), states that although genetic manipulation of mice has been possible for over two decades, the technology of nuclear transfer and homologous recombination has not been effective for the production of transgenic pigs.

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The specification does not teach the particulars of making a transgene construct wherein introduction of said transgene construct into a non-human animal produces a transgenic non-human animal; thus, the teachings of the art at the time the specification was filed must be relied upon for enablement. It is noted that the teachings of Lonberg et al (U.S. 5,545,806) can be applied to the production of a transgenic mouse having functional immunoglobulin transgenes. For the reasons set forth above, the application of the technology of making transgenic mice to the making of other non-human mammals is unreliable and unsuccessful. One of skill in the art would be subject to undue experimentation in order to make transgenic animals comprising the disclosed recombinant cells, and use said transgenic animals for the production of immunoglobulins expressed from the transgenes. Amendment of the claim17 and 18 to recite "isolated recombinant cell" and amendment of claims 19 and 20 to recite "growing a cell in vitro" would overcome this rejection.

10. Claims 17-20, 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Koho et al (Cancer Immunol Immunother, 1984, Vol. 17, pp. 165-172, reference BN of the IDS filed November 28, 2000). Claim 17 is drawn to a recombinant cell containing a recombinant nucleic acid comprising a nucleotide sequence encoding an antibody heavy chain which antibody competes for binding to CD40 with monoclonal antibody S2C6 and which protein increases the binding of the CD40 ligand to cell surface CD40 on B cells by at least 45%. Claim 18 is drawn to a recombinant cell containing a recombinant nucleic acid comprising SEQ ID NO:13, 14 and 15. Claim 19 is drawn to a method of producing an antibody heavy chain comprising growing a cell containing a recombinant nucleic acid encoding an antibody heavy chain which antibody competes for binding to CD40 with monoclonal antibody S2C6, which antibody increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% such that the antibody heavy chain is expressed in the cell, and recovering the antibody heavy chain. Claim 20 is drawn to a method of producing a protein comprising growing a cell containing a recombinant nucleic acid encoding a protein comprising SEQ ID NO:8, 9 and 10 such that said protein is expressed by the cell and recovering the expressed protein. Claim 61 embodies the recombinant cell of claim 18 wherein the nucleic acid comprises SEQ ID NO:6.

Claim 62 embodies the method of claim 20, wherein the recombinant nucleic acid encodes SEQ ID NO:7.

Koho et al disclose a hybridoma which secretes the S2C6 antibody (page 169, Table 3). The hybridoma is a recombinant cell because it comprises a myeloma cell fused to the spleen cell and the nucleic acids encoding the antibody in the spleen cell would not be present in the myeloma cell because said nucleic acid sequences are formed by recombination events within the spleen cell. Thus, the myeloma cell of the hybridoma would comprise a recombined nucleic acid not endogenous to said myeloma cell. Further, the specification states on page 18, lines 5-7 that the methods may include in vitro recombinant DNA and in vivo recombinants (genetic recombination). The genetic recombination event that produced the nucleic acids encoding the S2C6 antibody took place by means of a genetic recombination in vivo. Thus, the spleen cell comprising the nucleic acid encoding the S2C6 antibody can be considered as comprising recombinant nucleic acids due to a genetic rearrangement in vivo.

11. Applicant argues that the Written Description Guidelines Training materials indicate that due to the maturity of antibody technology, claims to antibodies meet the standard for written description. Applicant particularly points out Example 16 of the training materials. This has been considered but not found persuasive. The claim of example 16 is "An isolated antibody capable of binding to antigen X". The training materials states that "A review of the full content of the specification indicates that antibodies which bind to antigen X are essential to the operation of the claimed invention, and that the level of skill and knowledge in the art of antibodies at the time of filing was that production of antibodies against a well characterized antigen was conventional". The claim in the example is simply drawn to antibodies which bind an novel antigen. In the instant case there are many antibodies which bind to CD40 known in the prior art, including the S2C6 antibody itself, and applicant must set apart the genus of antibodies claimed from the antibodies of the prior art by means of functional and structural attributes. Further, the instant claims are drawn to isolated nucleic acid encoding this separate genus of antibodies. Thus, the fact pattern in the instant case substantially differs from example 16 of the written description guidelines wherein antigen X was novel and unobvious and the claims were drawn to antibodies which bind to said antigen. In order to meet this burden, applicant must

provide adequate written description of the claimed genus. Furthermore, in deference to the maturity of antibody-based technology, claims having no structural limitation for the antibody, but which comprise the limitation of competing for binding to CD40 with monoclonal antibody S2C6, were not rejected as lacking adequate written description. A review of the specification in light of the prior art indicates that binding to the S2C6 epitope on CD40 is crucial to the enablement of the instant invention. The specification teaches the administration of the antibodies encoded by the claimed nucleic acids for the treatment of cancer. The specification teaches that the binding of the S2C6 antibody increases the binding of the CD40 ligand to CD40. It is noted that applicant has decribed only one antibody to CD40, the binding of which elicits increased binding of the CD40 ligand. The art recognizes that the S2C6 can be modified to a chimeric, humanized ir single chained antibody by incorporation of the S2C6 paratope into other protein frameworks in order to retain binding specificity. However, it is expected that the epitope to which the paratope binds will remain the same. Thus, in light of the prior art, it is concluded that applicant has not described a genus of antibodies which would bind outside of the S2C6 epitope. The stucture of the S2C6 antibody or the epitope to which it binds does not adequately describe the structure of other antibodies which bind to CD40 and elicit an increase in the binding of the CD40 ligand because there is no correlation taught by the specification which would link the S2C6 eptiope to other eptiopes of the extracellular CD40 antigen, wherein binding of the other eptiope would elicit an increase in the binding of CD40 ligand. One of skill in the art would conlcude that applicant was not in possession of the genus of nucleic acids encoding the claimed antibodies.

12. All other rejections and objections as stated in Paper No. 7 are withdrawn.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703)

308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Art Unit 1642
10/27/03